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CAUSES AND TRIGGERS OF ASTHMA

It is not as simple to distinguish between the causes and triggers of asthma as might be expected. As a respiratory physician who only treats adults, I normally see asthmatic patients many years after the initiating events. For this presentation, I propose to discuss *causes*, by which I mean the genetic susceptibility and exposures which usually occur in early childhood, that lead to the development of asthma in the first place. I will then proceed to discuss *trigger factors* which can provoke an attack of asthma in someone who already has the condition. To complicate matters, some exposures are capable of acting both as causes and triggers.

Causes of asthma

A helpful model of the development of asthma is summarised in Fig. 1. Asthma comprises at least two underlying traits: allergy and bronchial hyperreactivity. Allergy is the tendency to produce excessive amounts of a particular type of antibody (IgE) in response to otherwise innocuous foreign proteins (allergens) in the environment. Bronchial hyperreactivity (BHR) is the tendency of the airways to narrow excessively in response to allergens or other nonspecific stimuli. Allergy and BHR are seen in most (but not all) patients with asthma.

Asthma genes. There is no doubt that asthma runs in families and some of the genes responsible for this have recently been discovered. Researchers in Oxford have identified mutations in one of the IgE receptor genes on the long arm of chromosome 11, which they claim are associated with allergies. Other groups have been unable to confirm these observations. We have found linkage between this location on chromosome 11 and BHR, rather than allergies (Van Herwerden et al. 1995). This suggests that other genes on chromosome 11 may be responsible for the susceptibility to asthma and the search for these genes is already underway.

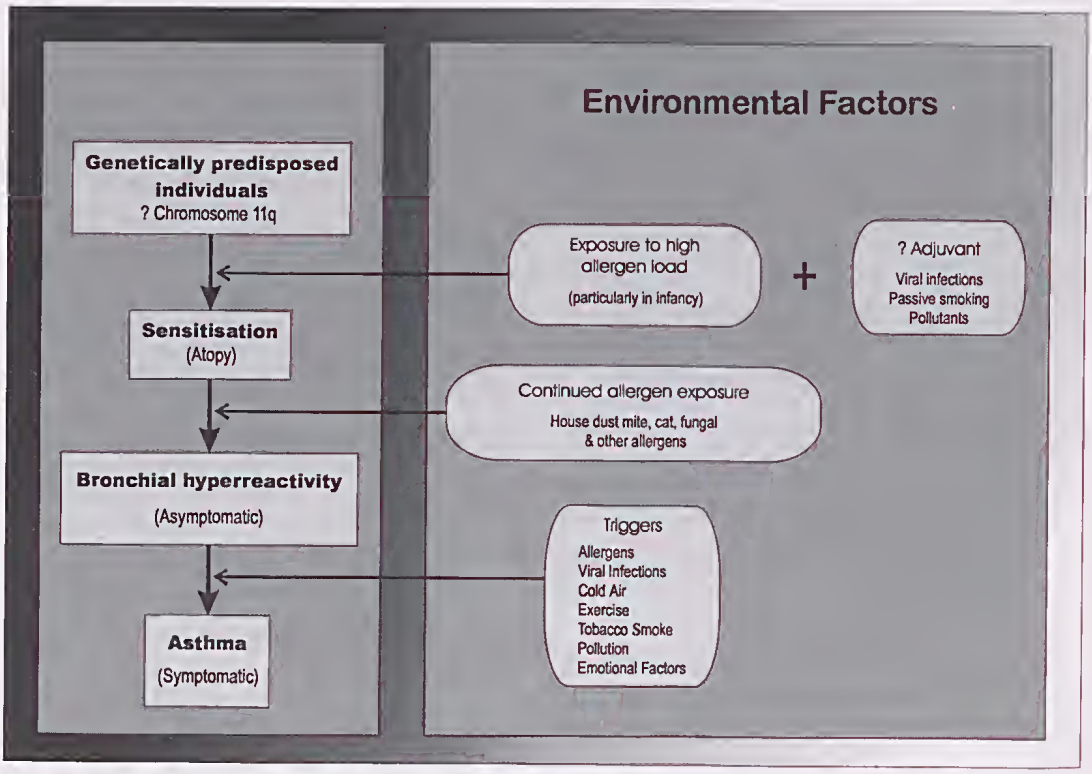

Fig. 1. Hypothesised progression from allergy to BHR to asthma.

There has also been considerable interest in a cluster of genes on the long arm of chromosome 5. Researchers at Johns Hopkins have found evidence for inheritance of high IgE levels in the Amish linked to a location near one particular gene (Interleukin 4) on this chromosome. Researchers at Southampton have found linkage between IgE levels and another gene (Interleukin 9) in this region. Furthermore, an American–Dutch collaboration has linked a nearby location to BHR in asthmatic families from the Netherlands. These exciting developments in the genetics of asthma have been well reviewed elsewhere (Wilkinson et al. 1996).

Childhood exposures. One of the complexities of asthma is that it arises from an interaction between the genes and environmental exposures, mostly occuring in infancy and early childhood. The developing immune systems of young children are bombarded with a wide variety of allergens in Western societies. These include the fine faecal particles of house dust mites, which are inevitable inhabitants of our bedding and carpets. New Zealand researchers have recently found astronomical levels of dust mite allergens in babies' sheepskin bedding. There is good evidence from Southampton that exposure to high levels of dust mites during the first month of life substantially increases the risk of developing dust mite allergy and asthma later in childhood (Warner & Warner 1996).

Pet ownership is common in Australia. Cat allergens are like the smile of the Cheshire cat; they hang around indoors for a long time after the cat has disappeared. Again the Southampton group has found that exposure to cats during the first month of life substantially increases the risk of developing cat allergy and asthma later in childhood. Contrary to popular belief, we now know that milk does *not* make mucus. However there is considerable interest in the role of dietary factors in the development of asthma. Children are now exposed to a wide variety of food additives from an early age. Recently it has been suggested that regular intake of oily fish may lessen the risk of asthma.

Occupational exposures. Although it commonly starts in childhood, asthma can begin at any age. Occupational asthma is a good example of the progression from susceptibility to allergy to BHR and symptoms. The causes can be classified as animal, vegetable, microbial or mineral (Newman-Taylor 1988). Susceptible laboratory workers who handle furry animals develop allergies and asthma in much the same way as children exposed to dust mite or cat allergens. A slightly different process occurs in carpenters exposed to western red cedar sawdust. In this situation, a small molecule needs to bind tissue proteins to set off an allergic reaction, which eventually results in asthma.

There are many other high risk occupations, such as aluminium smelting where occupational asthma has been recognised as a problem for 60 years, but the cause has not yet been identified. One of the key features of occupational asthma is the window of vulnerability. It is during the first few weeks of exposure in a new job that most cases of sensitisation arise. Another important concept is the minimum exposure dose and considerable effort has gone into defining safe exposure limits. Very high exposures to irritant gases such as sulphur dioxide or chlorine will result in a condition similar to occupational asthma, even in workers with no predisposing features.

Triggers of asthma

Some of the causes of asthma can also act as triggers for attacks, once the condition is established. This is certainly the case for house dust mite and cat allergens. On the other hand, air pollution doesn't cause asthma, but can probably trigger attacks. Many asthmatic patients are affected by a wide range of nonspecific irritants including cigarette smoke, perfume, hairspray and household bleach. Viral infections and exercise are common triggers for asthma attacks, particularly in children. The role of dietary factors is controversial.

Allergens. Once sensitisation has occurred, further exposure to allergens will trigger attacks of asthma. Thus we advise our dust mite allergic patients to avoid dusting or vacuuming. It was thought that exposure needed to exceed a threshold level of house dust mite allergen to produce symptoms, but there is now evidence of a dose response relationship at lower levels of exposure. The cartoon book *One hundred and one uses for a dead cat* was written by an asthmatic with severe cat allergy. Pollen allergic asthmatics are prone to dramatic seasonal attacks, which will be further discussed by Professor Knox.

I would like to share with you some fairly recent work on mould allergy. Researchers from the University of Sydney demonstrated that allergy to the mould *Alternaria* is the strongest risk factor for asthma among children in Wagga Wagga.

The strongest risk factor for asthma among young adults in Melbourne now appears to be allergy to the mould *Cladosporium*, the black mould many of you probably have growing in your bathrooms (Abramson et al. 1996). We have found higher levels of *Cladosporium* spores in the home of asthmatics and in the home of those with *Cladosporium* allergy than in the homes of nonallergic controls.

Air pollution. It is a popular misconception that the rising prevalence of asthma must be due to air pollution. In fact the prevalence of asthma is much lower in eastern Germany than in western Germany, whilst air pollution was unquestionably much worse in the east. However I wouldn't want you to conclude that air pollution has nothing to do with asthma. There have been some intriguing experiments suggesting that pre-exposure to ozone or nitrogen dioxide increases the response of the airways to allergens such as house dust mite or grass pollen (see Abramson et al. 1995). Both these gases are major constituents of photochemical smog, which certainly occurs in Sydney and Melbourne, although not to the same extent as in Los Angeles.

In Western societies, indoor air pollution probably results in more potential adverse health effects than outdoor air pollution. Nitrogen dioxide is also given off by unvented gas appliances and can accumulate in quite high concentrations indoors. A recent study in East Anglia found that gas cooking was associated with respiratory symptoms and impaired lung function in women, but not men (Jarvis et al. 1996). Other indoor pollutants which probably trigger asthma include woodsmoke and formaldehyde, which is released by foam insulation in mobile homes.

Cigarette smoking. There was an epidemic of cigarette smoking after World War II, which has only recently been brought under control. Active cigarette smoking was finally proved to cause lung cancer by the US Surgeon General in 1964 and chronic bronchitis and emphysema not long after. There is now a scientific consensus that passive smoking has deleterious effects in asthma (see Abramson et al. 1995). Furthermore, environmental tobacco smoke may act as a cofactor with allergens in the development of allergies in children. These were among the pieces of evidence cited by Justice Morling in his landmark ruling, which has seen smoking banished from most workplaces.

Viral infections. The most frequent triggers of asthma attacks are upper respiratory tract infections (or colds). New highly sensitive techniques have shown evidence of viral infections in over 80% of wheezing illnesses in children (see Abramson et al. 1995). Conversely wheezing has occurred in 50% of respiratory viral infections in asthmatics followed prospectively. Although many studies have suggested an association between early respiratory illness and asthma, it is not at all certain that this is the cause and effect. Indeed there is some evidence that early respiratory infections may protect against the subsequent development of allergies.

Dietary factors. Many patients with asthma report that particular foods worsen their condition. However these reports are notoriously difficult to confirm with placebo controlled double blinded food challenges. The parents of asthmatic children frequently attempt dietary modification, with little objective evidence of benefit. There are well documented reports of asthma attacks following the ingestion of food additives such as tartrazine and metabisulphite. Monosodium glutamate (MSG) which is used as a flavour enhancer in Chinese food, has received bad press as a trigger for asthma, but does not seem to have much effect on lung function tests performed in our laboratory. On the other hand, so-called 'natural' products such as Royal Jelly can cause life threatening allergic reactions in asthmatics.

Exercise. Exercise particularly in cold dry air is a potent trigger of asthma attacks. This is the reason that many asthmatic children have been encouraged to take swimming lessons. Warm moist air is much less likely to trigger attacks. It is thought that cold air dries out the lining of the airways causing the release of chemicals such as histamine, which make the muscles surrounding the airways contract and bring about an attack of asthma. These attacks can be effectively prevented by premedication.

Prospects for prevention of asthma

To prevent asthma developing in the first place will require much more knowledge of the underlying causes. The recent advances in genetics will hopefully allow us to more accurately identify infants at a high risk of developing the condition. The environmental modifications required are likely to include a major redesign of Western style housing. Occupational asthma can be prevented by substitution of safer chemicals and control of

workplace exposures. The prevention of attacks in people who already have asthma will be discussed by Dr Pierce.

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DON CAMPBELL

WHO GETS ASTHMA? WHO DIES FROM IT?

Summary

The prevalence of asthma in Australia has risen in recent years. The prevalence of current asthma in South Australia rose from 5.6% to 9.0% between 1987 and 1990. In 1994 the cumulative prevalence of asthma in the Australian population was 15.3%. Studies of asthma prevalence in 8- to 11-year-olds conducted in the same community demonstrate a rise in prevalence of current asthma from 6.5% to 9.9% between 1982 and 1992, and a rise in the cumulative prevalence of diagnosed asthma from 12.9% to 19.3%.

Genetic factors are important in the development of asthma and atopy, however environmental factors appear to be crucial to the onset and persistence of asthma. These factors include changes in the indoor levels of house dust mite, levels of oxides of nitrogen and possibly diet (oily fish intake). Up to two-thirds of asthmatic children continue to suffer from asthma through puberty and into adult life. Five to 10% of children with mild asthma are likely to develop severe asthma in later life. Children with moderate to severe asthma are at risk of long-term effects of asthma throughout life.

The age-adjusted asthma mortality rate in Australia increased from 2.7/100 000 in 1971 to 4.85 in 1989, declining to 3.53 in 1992. Between 1981 and 1992, for the very young (<15 years) the mortality rate was very low (<1/100 000) with little evidence of a change. For intermediate age ranges there was evidence of an initial rise and a subsequent reduction in mortality rates, whilst in the elderly mortality rates from asthma continue to rise. The positive predictive value of death certification due to asthma is very accurate in the under 55 age group, whilst in the over 64 age group the death certificate is not current enough to be used for epidemiological purposes.

Causative factors to explain the rise in mortality due to asthma may include the increased size of the at-risk population (prevalence), or a change in the severity of asthma. Detailed analyses indicate a large burden of preventable mortality due to asthma which reflects poor management including failure to recognise the severity of asthma, failure to manage asthma appropriately and poor compliance with asthma management plans.

Definition

> 'Asthma is a chronic inflammatory disorder of the airways in which many cells play a role. In susceptible individuals this inflammation causes symptoms which are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. It also causes an associated increase in airway responsiveness to a variety of stimuli.'
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> *From the international consensus report on diagnosis and treatment of asthma, 1992.*

1. *Prevalance of asthma*

The prevalence of asthma in Australia has risen in recent years. The prevalence of current asthma in South Australia rose from 5.6% to 9.0% between 1987 and 1990. In 1992 the prevalence of current asthma in Victorian adults was shown to be 7%. In 1994 the cumulative prevalence of asthma in the Australian adult population was 15.3%.